Criteria for Use of Linezolid (Zyvox™), Quinupristin-dalfopristin (Synercid®), and Daptomycin (Cubicin™)

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Due to the high specificity of these antibiotics and the potential for the development of resistance, each facility should define a system for approval for use of linezolid, quinupristin-dalfopristin, and daptomycin to avoid overuse. These antibiotics should only be used in consultation with an Infectious Disease (ID) specialist, except when consultation is not available in a timely manner. Use of these antibiotics should generally be reserved for serious infections for which there are no alternative antimicrobial therapy. Treatment of such infections begins with abscess drainage, and with the removal of suspected IV, intra-arterial, or urethral catheters.

Criteria for VA use

Vancomycin-resistant *Enterococcus faecium*: Proven, serious infections (not colonization) [a]	Linezolid Quinupristin-dalfopristin Daptomycin[b]
Vancomycin-resistant *Enterococcus faecalis*: Proven, serious infections (not colonization) **AND** allergy to, resistance to, or failed treatment with ampicillin[c]	Linezolid Daptomycin[b]
Methicillin-resistant *S. aureus* (MRSA) [d]: Complicated skin or skin-structure infections (cSSSI) **AND one or more of the following:** • Proven vancomycin resistance • Infection in patients who are intolerant of vancomycin secondary due to true vancomycin allergy or to serious adverse drug reaction to vancomycin • Failed treatment with vancomycin • For oral linezolid only: patients suitable for oral therapy form whom therapy with oral trimethoprim-sulfamethoxazole, tetracyclines, fluoroquinolones and clindamycin is inappropriate due to microbial resistance or patient intolerance of these medications.	Linezolid Daptomycin Quinupristin-dalfopristin[e]
Methicillin-resistant *S. aureus* (MRSA) [d,f,g] MRSA nosocomial pneumonia	Linezolid[h]

a. For VRE, combination with other agents may be required depending on the site of infection.
b. Daptomycin –VRE susceptible *in vitro*; has been studied in ~20 patients (Data on file-Cubist)
c. Quinupristin-dalfopristin is not active against *E. faecalis*
d. Clindamycin, co-trimoxazole, and doxycycline or minocycline are treatment options for some mild-moderate MRSA infections. Clindamycin should be used only if there is no evidence of inducible resistance to clindamycin in the presence of erythromycin. Tetracycline resistant MRSA may have inducible doxycycline resistance that is not apparent upon routine doxycycline or minocycline susceptibility testing (Trzcinski 2001).
e. Quinupristin-dalfopristin is not approved for cSSSI due to MRSA; MRSA susceptible *in vitro*; has been used in a small number of patients in the clinical setting (Nichols 1999, Drew 2000)
f. Daptomycin should not be used to treat pneumonia due to poor intra-alveolar activity
g. Quinupristin-dalfopristin is not FDA approved to treat pneumonia nor is it approved to treat infections due to MRSA. It has been used to treat MRSA pneumonia in the clinical setting. In 38 evaluable patients, the cure rate was 31% and 44.4% for quinupristin-dalfopristin and vancomycin respectively. (Fagon 2000)
h. Linezolid is approved to treat MRSA pneumonia. Although retrospective analysis of 2 studies suggested superiority of linezolid to vancomycin, (Wunderink 2003), these data require confirmation before linezolid can be recommended as first-line therapy for patients with MRSA pneumonia (Stevens 2002).

OTHER USES

1. These agents are not approved by the FDA for treatment of MRSA or VRE endocarditis or bone/joint infections. There are limited data from patients who have been treated as part of compassionate use programs and from case reports.

2. In vitro studies, animal model and pharmacodynamic model studies, and clinical case reports suggest that quinupristin-dalfopristin may be useful as part of synergistic combination regimens for MRSA. Therefore, there may be a role for quinupristin-dalfopristin when usual synergistic combinations have failed or are not tolerated. Because of *in vitro* reports of antagonism or indifference, synergy testing and consultation with an ID specialist is recommended before considering such therapies. (Brown 2004)

3. To complete a course of IV therapy (vancomycin, linezolid, quinupristin-dalfopristin) with oral linezolid (Li 2001). Oral use of clindamycin, co-trimoxazole, a fluoroquinolone, doxycycline or minocycline are treatment options for some mild-moderate MRSA infections. Clindamycin should be used only if there is no evidence of inducible resistance to clindamycin in the presence of erythromycin. For a switch to oral therapy, the patient must be:

   - Afebrile
   - Clinically improved
   - Able to take oral medications
   - Have adequate home support and clinical followup

   At the present time, there is not enough data on the use of oral linezolid in osteomyelitis and endocarditis

4. Vancomycin resistant enterococci have been associated with asymptomatic bacteriuria and colonization of the urinary tract. Antibiotics are frequently not necessary once the urinary catheter is removed. If antibiotics are deemed necessary, agents such as nitrofurantoin can be used. Linezolid should not be routinely used in this setting.

TOXICITIES AND WARNINGS

Linezolid

Myelosuppression has been reported in patients receiving linezolid. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop anemia, leukopenia, pancytopenia, or thrombocytopenia.

Other toxicities and adverse events include peripheral neuropathy, optic neuritis, lactic acidosis and monoamine oxidase inhibition (Wigen 2003)..

Quinupristin-dalfopristin

Quinupristin-dalfopristin is a significant inhibitor of cytochrome P450 3A4. Co-administration of quinupristin-dalfopristin with drugs that are substrates of CYP 3A4 and possess a narrow therapeutic window requires caution and monitoring. Co-administration of medications metabolized by CYP 3A4 that prolong QTc interval should be avoided.

Quinupristin-dalfopristin diluted in 250cc of D5W is administered by peripheral IV infusion. If moderate or severe venous irritation occurs, the infusion volume can be increased to 500 or 750cc or it can be administered via a central line or peripherally inserted central catheter (PICC).

Daptomycin

The manufacturer recommends that patients be monitored for muscle pain or weakness, particularly of the distal extremities and to obtain weekly CPK levels while on therapy. Patients developing unexplained CPK elevations should be monitored more frequently; however, those with substantially elevated CPK (≥ 10 X ULN) should discontinue daptomycin. Daptomycin should also be discontinued in those who have unexplained symptoms of myopathy and elevated CPK. It is suggested that HMG-CoA reductase inhibitors be temporarily discontinued while receiving daptomycin.

DOSE

	Dose
Linezolid	600mg q 12 hours
Quinupristin-dalfopristin*	7.5mg/kg q 8 hours
Daptomycin	4mg/kg q 24 hours

*Dose for treating VREF

COST

	FSS cost per vial
Linezolid*	600mg vial= $48.40
Quinupristin-dalfopristin	500mg vial= $71.27 600mg vial= $86.95
Daptomycin	500mg vial = $100.67

*The price of oral linezolid 600mg is $35.31 per tablet
Prices as of 7/04

REFERENCES

Vancomycin-resistant enterococcus

Moellering RC, Linden PK, Reinhardt J, et al. The efficacy and safety of quinupristin-dalfopristin for the treatment of infections caused by vancomycin resistant enterococcus faecium. J Antimicrob Chemother 1999; 44: 251-261.

Raad Issam, Hachem R, Hanna H, et al. Treatment of vancomycin-resistant enterococcal infections in the immunocompromised host: quinupristin-dalfopristin in combination with minocycline. Antimicrob Agents Chemother 2001; 45: 3202-3204.

Winston DJ, Emmanouilides, Kroeber A, et al. Quinupristin-dalfopristin therapy for infections due to vancomycin-resistant enterococcus faecium. Clin Infect Dis 2000; 30: 790-797.

Linden PK, Moellering RC, Wood CA, et al. Treatment of vancomycin-resistant enterococcus faecium infections with quinupristin-dalfopristin. Clin Infec Dis 2001; 33: 1816-1823.

El Khoury J, Fishman JA. Linezolid in the treatment of vancomycin-resistant enterococcus faecium in solid organ transplant recipients: report of a multicenter compassionate-use trial. Transplant Infect Dis 2003; 5: 121-125.

Raad I, Hachem R, Hanna H, et al. Prospective, randomized study comparing quinupristin-dalfopristin with linezolid in the treatment of vancomycin-resistant Enterococcus faecium infections. J Antimicrob Chemother 2004; 53: 646-649.

cSSSI trials

Nichols RL, Graham DR, Barriere SL, et al. Treatment of hospitalized patients with complicated gram-positive skin and skin structure infections: two randomized, multicenter studies of quinupristin/dalfopristin verus cefazolin, oxacillin or vancomycin. J Antimicrob Chemother 1999; 44: 263-273.

Methicillin-resistant staphylococcus

Drew RH, Perfect JR, Srinath L, et al. Treatment of methicillin-resistant staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. J Antimicrob Chemother 2000: 46: 775-784.

Moise PA, Forrest A, Birmingham MC, et al. The efficacy and safety of linezolid as treatment fror staphylococcus aureus infections in compassionate use patients who are intolerant of, or who have failed to respond to vancomycin. J Antimicrob Chemother 2002; 50: 1017-1026.

Wunderink RG, Rello J, Cammarata SK, et al. Analysis of two double-blind studies of patients with methicillin-resistant staphylococcus aureus nosocomial pneumonia. Chest 2003; 124: 1789-1797.

Stevens DL, Herr D, Lampiris H, et al. Linezolid versus vancomycin for the treatment of methicillin-resistant staphylococcus aureus infections. Clin Infect Dis 2002; 34: 1481-1490.

Fagon JY, Patrick H, Haas DW, et al. Treatment of gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Am J Respir Crit Care Med 2000; 161: 753-762.

Parodi, S, Rhew DC, Goetz MB. Early switch and early discharge opportunities in intravenous vancomycin treatment of suspected methicillin-resistant staphylococcal species infection. J Managed Care Pharm 2003; 9(4): 317-326.

Li Z, Willke RJ, Pinto LA, et al. Comparison of length of hospital stay for patients with known or suspected methicillin-resistant staphylococcus species infections treated with linezolid or vancomycin and randomized, multicenter trial. Pharmacotherapy 2001; 21(3): 263-274.

Howden BP, Ward PB, Charles PGP, et al. Treatment outcomes for serious infections caused by methicillin-resistant staphylococcus aureus with reduced vancomycin susceptibility. Clin Infect Dis 2004; 38: 521-528.

Trzcinski K, Cooper BS, Hryniewicz W, Dowson CG. Expression of resistance to tetracyclines in strains of methicillin-resistant Staphylococcus aureus. J Antimicrob Chemother. 2001 Feb;47(2):239-40

Other

Brown J, Freeman BB. Combining quinupristin-dalfopristin with other agents for resistant infections. Ann Pharmacother 2004; 38: 677-685.

Rayner CR, Baddour LM, Birmingham MC, et al. Linezolid in the treatment of osteomyelitis: results of compassionate use experience. Infection 2004; 32 : 8-14

Wigen CG, Goetz MB. Serotonin Syndrome and Linezolid. Clin Infect Dis. 2002;34:1651-1652.

Synercid product package insert. July 2003

Cubicin product package insert. September 2003

Zyvox product package insert. November 2003